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(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM P.L.C. [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: BROOKS, Gerald [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). HUNT, Eric [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).

(74) Agent: CONNELL, Anthony, Christopher; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

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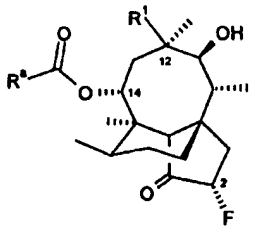
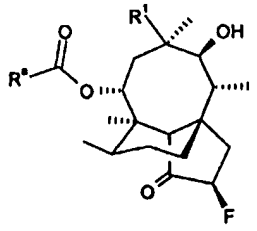


(a)



(b)

(57) Abstract

A 14-acyloxy derivative of mutilin or 19,20-dihydromutilin having a 2-fluoro substituent of structure (a), (b), in which R^1 is vinyl or ethyl, and R^a.CO.O- is an acyloxy group. The acyloxy group may be $HOCH_2CO_2$- or R-X-CH_2CO_2-, or R^2-$(CH_2)_m$-X-$(CH_2)_n$-CH_2CO_2- or carbamoyl. The compounds are useful for treating microbial infections in animals, especially in humans and in domesticated mammals.

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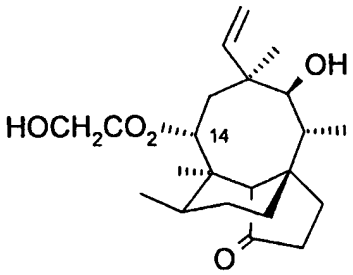
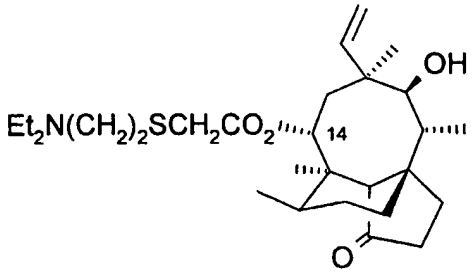
2-FLUORO MUTILIN DERIVATIVES

The present invention relates to novel compounds, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medical therapy, particularly antibacterial therapy.

Pleuromutilin, the compound of formula (A), is a naturally occurring antibiotic which has antimycoplasmal activity and modest antibacterial activity. It has been shown that the antimicrobial activity can be improved by replacing the glycolic ester moiety at position 14 by another acyloxy group R-X-CH_2CO_2-, where R is an aliphatic or aromatic moiety and X is O, S, or NR' (H Egger and H Reinshagen, J Antibiotics, 1976, 29, 923). Tiamulin, the compound of formula (B), which is used as a veterinary antibiotic, is a derivative of this type (G Hogenauer in Antibiotics, Vol. V, part 1, ed. F E Hahn, Springer-Verlag, 1979, p.344).



(A)



(B)

In this application, the non-conventional numbering system which is generally used in the literature (G Hogenauer, loc.cit.) is used.

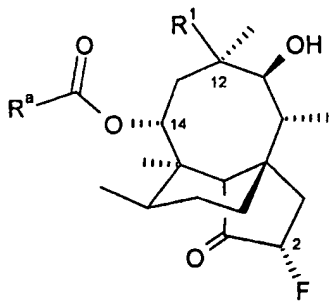
WO 97/25309 (SmithKline Beecham) describes further modification of the acyloxy group, disclosing 14-*O*-carbamoyl derivatives of mutilin or 19, 20-dihydromutilin, in which the N-atom of the carbamoyl group is unsubstituted, mono- or di-substituted.

WO98/05659 (SmithKline Beecham) discloses 14-*O*-carbamoyl derivatives of mutilin or 19, 20-dihydromutilin, in which the N-atom of the carbamoyl group is acylated by a group which includes an azabicyclic moiety.

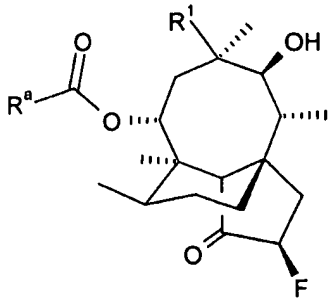
We have now surprisingly discovered that novel pleuromutilin analogues having a fluorine substituent on the nucleus have good antibacterial activity combined with improved metabolic stability.

Accordingly in its broadest aspect the present invention provides a 14-acyloxy derivative of mutilin or 19,20-dihydromutilin having a 2-fluoro substituent.

The 2-fluoro compounds of the invention may of (2*S*) configuration or the (2*R*) configuration, or mixtures thereof. The (2*S*) configuration is preferred. The structure of the two isomers is as follows



(2*S*)-2-Fluoro



(2*R*)-2-Fluoro

in which R^1 is vinyl or ethyl, and R^a.CO.O- is an acyloxy group.

The acyloxy group may be $HOCH_2CO_2$-, as in pleuromutilin, or R-X-CH_2CO_2-, where X is O, S, or NR' and R and R' are individually hydrogen or an aliphatic or aromatic moiety as in the compounds of Egger and Reinshagen.

Alternatively the acyloxy group may be R^2-$(CH_2)_m$-X-$(CH_2)_n$-CH_2CO_2- where each of n and m is independently from 0 to 2;
X is selected from -O-, -S-, -S(O)-, -SO_2-, -NH-, CONH-, -CH_2-, and a bond; and
R^2 is a non-aromatic monocyclic or bicyclic group containing one or two basic nitrogen atoms and attached through a ring carbon atom.

R^2 , when monocyclic can contain from 4 to 8 ring atoms, and when bicyclic can contain from 5 to 10 ring atoms in each ring, and is optionally substituted on carbon by up to 3 substituents. Suitable substituents include alkyl, alkyloxy, alkenyl and alkenyloxy, each

of which may be carried by either a bridgehead or a non-bridgehead carbon atom. In addition, the or each nitrogen atom may be substituted by oxygen, to form an N-oxide, or by mono- or dialkyl, in which case it will be appreciated that a quaternary cation can be formed. The counterion may be a halide ion such as chloride or bromide, preferably chloride. The aza ring system additionally may contain one or more double bonds.

Preferably the acyloxy group is carbamoyl, especially $R^3R^4NCO_2$-

in which:

R^3 and R^4 are the same or different groups selected from

hydrogen;

a straight or branch chained, saturated or unsaturated, optionally substituted, C_1 to C_6 hydrocarbon group;

a saturated or unsaturated, optionally substituted, C_3 to C_8 cyclic hydrocarbon group;

an optionally substituted heterocyclic group;

an optionally substituted aryl group;

or together form an optionally substituted cyclic group of 3 to 8 ring atoms, optionally, containing one additional heteroatom selected from N, O and S, and optionally fused to a hydrocarbon ring, a heterocyclic group or an aromatic group; or

R^3 is one of the above monovalent groups and R^4 is a group selected from SO_2R^5, COR^6, OR^6 and NR^7R^8 where

R^5 is selected from a straight or branch chained, saturated or unsaturated, optionally substituted, C_1 to C_6 hydrocarbon group; a saturated or unsaturated, optionally substituted, C_3 to C_8 cyclic hydrocarbon group; an optionally substituted heterocyclic group; an optionally substituted aryl group; an optionally substituted C_1 to C_6 alkyl amino group; and an optionally substituted aryl amino group;

R^6 is selected from hydrogen; a straight or branch chained, saturated or unsaturated, optionally substituted, C_1 to C_6 hydrocarbon group; a saturated or unsaturated, optionally substituted, C_3 to C_8 cyclic hydrocarbon group; an optionally substituted heterocyclic group; and an optionally substituted aryl group;

R^7 and R^8 are the same or different groups selected from hydrogen; a straight or branch chained, saturated or unsaturated, optionally substituted, C_1 to C_6 hydrocarbon group; a saturated or unsaturated, optionally substituted, C_3 to C_8 cyclic hydrocarbon group; an optionally substituted heterocyclic group, and an optionally substituted aryl group; or together form an optionally substituted cyclic group of 3 to 8 ring atoms, optionally containing one additional heteroatom selected from N, O and S, and optionally fused to a hydrocarbon ring, a heterocyclic group or an aromatic group.

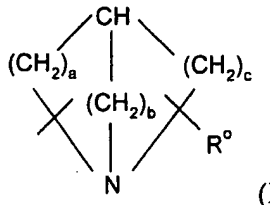
Particularly suitable values for R^3 and R^4 are hydrogen, hydroxy, methoxy, phenyl, methyl, *iso*-propyl, phenylsulphonyl, methoxyphenyl, nitrophenyl, trichloroacetyl, benzyl, hydroxyiminobenzyl, benzylamino-sulfonyl, dichloropyridinyl, hydroxyethyl, 2-phenylethyl, 1-(R)-phenyl-2-hydroxyethyl, 2-(methoxycarbonyl)ethyl, 2-carboxyethyl, dimethylamino, dimethylaminopropyl, methanesulphonylamino, methanesulphonyl, benzoylamino, benzoyl optionally substituted by trifluoromethyl, carboxy, methoxy, hydroxy, acetoxy, amino or nitro, furoyl, nicotinoyl, *iso*nicotinoyl, acetyl, phenylacetyl, and phenoxy. Particularly suitable values for cyclic groups R^3R^4N are indolino and morpholino.

Advantageously the N-atom of the carbamoyl group is acylated by a group which includes an azabicyclic moiety. More specifically the acyloxy group is advantageously $R^9CONHCO_2$- in which R^9 is a group R^{10}, $R^{10}CH_2$-, or $R^{11}R^{12}C$=CH-; wherein R^{10} is an azabicyclic ring system or R^{11} and R^{12} together with the carbon atom to which they are attached form an azabicyclic ring system.

The azabicyclic ring system may be a bridged or fused non-aromatic ring system attached via a bridgehead or non-bridgehead ring carbon atom and containing one bridgehead nitrogen atom as the sole hetero ring atom. The ring system contains between 5 and 10

ring atoms in each ring and is optionally substituted on carbon by up to 3 substituents. Suitable substituents include alkyl, alkyloxy, alkenyl and alkenyloxy, each of which may be carried by either a bridgehead or a non-bridgehead carbon atom. In addition, the bridgehead nitrogen atom may be substituted by oxygen, to form an N-oxide, or by alkyl, to form a quaternary cation. The counterion may be a halide ion such as chloride or bromide, preferably chloride.

The azabicyclic ring system may for example be represented by formula (I):



(I)

wherein R^o represents one or more optional substituents as set out above and each of a, b and c is between 0 and 4, such that any one ring has between 5 and 10 ring atoms. The azabicyclic ring system additionally may contain one or more double bonds.

Particular azabicyclic groups include azabicyclo[2.2.2]octyl, azabicyclo[2.2.1]heptyl, azabicyclo[3.2.1]octyl, azabicyclo[4.4.0]decyl, quinuclidinyl, azabicyclo[3.2.1]octenyl, and azabicyclo[3.3.1]non-5-yl.

Suitable C_1 to C_6 hydrocarbon groups include straight and branched chain alkyl groups having from 1 to 6 carbon atoms, for instance methyl, ethyl, *n*-propyl and *iso*-propyl, preferably methyl. Suitable C_3 to C_8 cyclic hydrocarbon groups include cycloalkyl such as cyclopropyl, cyclopentyl and cyclohexyl.

When used herein, the term "heteroaryl" includes aromatic single and fused rings containing up to four heteroatoms in each ring, each of which is selected from oxygen, nitrogen and sulphur, which rings may be unsubstituted or substituted by, for example, up to three substituents. Each heteroaryl ring suitably has 5 or 6 ring atoms. A fused heteroaryl ring may include carbocyclic rings and need include only one heteroaryl ring.

Preferably a substituent for a heteroaryl or a heterocyclyl group is selected from halogen, (C_{1-6})alkyl, aryl(C_{1-4})alkyl, (C_{1-6})alkoxy, (C_{1-6})alkoxy(C_{1-6})alkyl, halo(C_{1-6})alkyl, hydroxy, amino, mono- and di-*N*-(C_{1-6})alkyl-amino, acylamino, carboxy salts, carboxy esters, carbamoyl, mono- and di-*N*-(C_{1-6})alkylcarbonyl, aryloxycarbonyl, (C_{1-6})alkoxycarbonyl(C_{1-6})alkyl, aryl, oxy groups, ureido, amidino, guanidino, sulphonylamino, aminosulphonyl, (C_{1-6})alkylthio, (C_{1-6})alkylsulphinyl, (C_{1-6})alkylsulphonyl, heterocyclyl and heterocyclyl(C_{1-4})alkyl.

Alkyl and alkenyl groups referred to herein include straight and branched groups containing up to six carbon atoms and are optionally substituted by one or more groups selected from the group consisting of aryl(C_{1-6})alkoxy, aryl(C_{1-6})alkylthio, cycloalkyl, cycloalkenyl, carboxy and salts and esters thereof, halogen, hydroxy, (C_{1-6})alkoxy, aryloxy, (C_{1-6})alkoxycarbonyl, carbamoyl, mono- or di(C_{1-6})alkylcarbamoyl, sulphamoyl, mono- and di(C_{1-6})alkylsulphamoyl, amino, mono- and di(C_{1-6})alkylamino, (C_{1-6})acylamino, ureido, (C_{1-6})alkoxycarbonylamino, aryl, heterocyclyl, oxo, hydroxyimino, acyl, (C_{1-6})alkylthio, arylthio, (C_{1-6})alkane-sulphinyl, arylsulphinyl, (C_{1-6})alkanesulphonyl, arylsulphonyl, amidino, amidoxime and guanidino.

Cycloalkyl and cycloalkenyl groups referred to herein include groups having between three and eight ring carbon atoms and are optionally substituted as described hereinabove for alkyl and alkenyl groups.

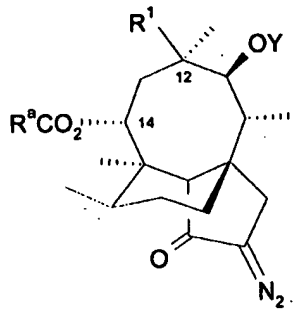
When used herein, the term "aryl" means single and fused rings suitably containing from 4 to 7, preferably 5 or 6, ring atoms in each ring, which rings, may each be unsubstituted or substituted by, for example, up to three substituents. A fused ring system may include aliphatic rings and need include only one aromatic ring. Suitable aryl groups include phenyl and naphthyl such as 1-naphthyl or 2-naphthyl. Suitably any aryl group, including phenyl and naphthyl, may be optionally substituted by up to five, preferably up to three substituents. Suitable substituents include halogen, (C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, (C_{1-6})alkoxy, (C_{1-6})alkoxy(C_{1-6})alkyl, halo(C_{1-6})alkyl, aryl(C_{1-6})alkoxy, hydroxy, nitro, cyano, azido, amino, mono- and di-*N*-(C_{1-6})alkylamino, acylamino,

arylcarbonylamino, acyloxy, carboxy, carboxy salts, carboxy esters, carbamoyl, mono- and di-*N*-(C_{1-6})alkylcarbamoyl, (C_{1-6})alkoxycarbonyl, aryloxycarbonyl, ureido, guanidino, sulphonylamino, aminosulphonyl, (C_{1-6})alkylthio, (C_{1-6})alkyl sulphinyl, (C_{1-6})alkylsulphonyl, heterocyclyl and heterocyclyl (C_{1-6})alkyl. In addition, two adjacent ring carbon atoms may be linked by a (C_{3-5})alkylene chain, to form a carbocyclic ring.

When used herein the terms "heterocyclyl" and "heterocyclic" suitably include, unless otherwise defined, aromatic and non-aromatic, single and fused, rings suitably containing up to four heteroatoms in each ring, each of which is selected from oxygen, nitrogen and sulphur, which rings, may be unsubstituted or substituted by, for example, up to three substituents. Each heterocyclic ring suitably has from 4 to 7, preferably 5 or 6, ring atoms. A fused heterocyclic ring system may include carbocyclic rings and need include only one heterocyclic ring.

Preferably a substituent for a heterocyclyl group is selected from halogen, (C_{1-6})alkyl, aryl(C_{1-6})alkyl, (C_{1-6})alkoxy, (C_{1-6})alkoxy(C_{1-6})alkyl, halo(C_{1-6})alkyl, hydroxy, amino, mono- and di-*N*-(C_{1-6})alkyl-amino, acylamino, carboxy, carboxy salts, carboxy esters, carbamoyl, mono- and di-*N*-(C_{1-6})alkylcarbonyl, aryloxycarbonyl, (C_{1-6})alkoxycarbonyl(C_{1-6})alkyl, aryl, oxy groups, ureido, guanidino, sulphonylamino, aminosulphonyl, (C_{1-6})alkylthio, (C_{1-6})alkylsulphinyl, (C_{1-6})alkylsulphonyl, amidino, amidoxime, heterocyclyl and heterocyclyl(C_{1-6})alkyl.

In a further aspect the present invention provides a method for preparing compounds of the invention which comprises reacting a 14-acyloxy-2-diazo derivative of mutilin or 19,20-dihydromutilin, preferably protected at the 11-hydroxy position, such as a compound of formula



where R^1 is ethyl or vinyl, R^a.CO.O- is an acyloxy group, and Y is hydrogen or a removable hydroxy-protecting group,
with a source of hydrogen fluoride.

Conveniently, the hydrogen fluoride source is an amine complex of hydrogen fluoride (*e.g.* hydrogen fluoride-pyridine, hydrogen fluoride 2,4,6-trimethylpyridine; hydrogen fluoride triethylamine; or poly-4-vinylpyridinium poly(hydrogen fluoride)). The reaction may be carried out in an anhydrous solvent (*e.g.* diethyl ether, tetrahydrofuran, 1,2-dimethoxyethane) at a temperature of -15°C to 25°C.

This reaction produces (2*S*)-2-fluoro derivatives. (2*R*)-2-Fluoro-mutilin derivatives may be prepared by treating the (2*S*)-isomer with a base (*e.g.* sodium hydroxide or potassium hydroxide in ethanol). This will usually produce a mixture of (2*S*) and (2*R*)-isomers that may be separated using conventional techniques such as chromatography and crystallisation.

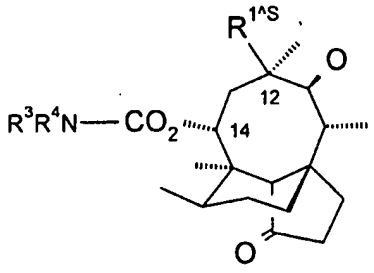
2-Diazo-mutilin derivatives may be prepared using the method described by H Berner, G Schulz, and G Fisher, *Monatsh. Chem.*, 1981, **112**, 1441, for example reacting a solution of a 2-hydroxymethylene-14-acyloxy-mutilin or 2-hydroxymethylene-11-formate-14-acyloxy-mutilin derivative in dichloromethane at -10 °C under argon with tosylazide and triethylamine.

2-Hydroxymethylene-14-acyloxy-mutilin and the 11-formate may be prepared using procedures based on that described by A.J. Birch, C.W. Holzapfel and R.W. Rickards (Tet (Suppl) 1996 8 part III 359) in which the corresponding 14-acyloxy-mutilin derivative in toluene and methyl formate is treated with sodium methoxide and stirred

under argon. The formate group may be removed when desired by treatment with potassium hydroxide in methanol.

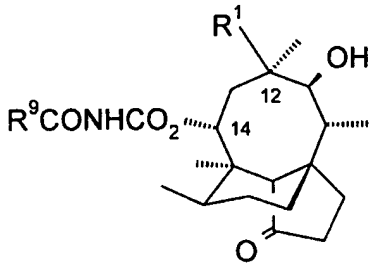
The 14-acyloxy-mutilin derivative may be pleuromutilin or a compound substituted at position 14 by another acyloxy group R-X-CH_2CO_2- , prepared as disclosed by H Egger and H Reinshagen, J Antibiotics, 1976, 29, 923.

Additionally, the 14-acyloxy-mutilin derivative may be a 14-*O*-carbamoyl derivative, especially a compound of formula (1)



(1)

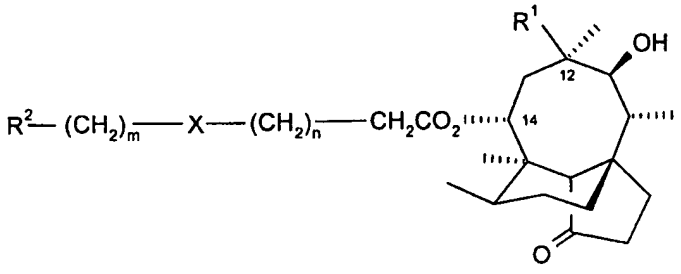
prepared as in WO 97/25309 (SmithKline Beecham) or



(2)

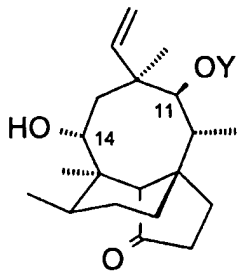
prepared as in WO98/05659 (SmithKline Beecham)

Also the 14-acyloxy-mutilin derivative may be a compound of general formula (3):

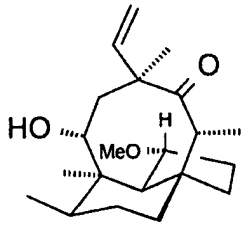


(3)

prepared by reacting a compound of formula (4) where Y is hydrogen or a hydroxyl protecting group, such as an acyl group, or a compound of formula (5), with an acylating agent formed from a carboxylic acid of formula R^2-$(CH_2)_m$-X-$(CH_2)_n$-CH_2CO_2H:



(4)



(5)

General methods for forming esters by this type of procedure are described by I O Sutherland in *Comprehensive Organic Chemistry*, Vol. 2, ed. I O Sutherland, pages 875-883 (Pergamon Press, Oxford, 1979). The acylating agent, formed from the carboxylic acid of formula R^2-$(CH_2)_m$-X-$(CH_2)_n$-CH_2CO_2H , can be the acid chloride, acid bromide, a mixed anhydride, or an *N*-acyl-imidazole. The preferred agent is the acid chloride. General methods for forming such acylating agents are described in the chemical literature (see I O Sutherland, *loc. cit.*, and references therein).

The ester-forming reaction can be carried out in the presence of an organic base, an inorganic base, or an acid. Organic bases include pyridine, 2,6-lutidine, triethylamine, and *N,N*-dimethylaniline. Inorganic bases include sodium hydride, lithium hydride, potassium carbonate, lithium hexamethyldisilazide, and sodium hexamethyldisilazide. Acids include *p*-toluenesulphonic acid, benzene sulphonic acid, and sulphuric acid. Optionally, when the reaction is carried out in the presence of a base, an acylation catalyst (G Hofle and W Steglich, *Synthesis*, 1972, 619) such as 4-dimethyamino-pyridine or 4-pyrrolidino-pyridine may also be added to the reaction mixture. Solvents for the ester forming reaction include tetrahydrofuran, 1,4-dioxane, acetonitrile, *N,N*-dimethylformamide, diethyl ether, dichloromethane, and chloroform. A preferred solvent is tetrahydrofuran.

Although it is possible to prepare compounds of formula (3) by reaction at the 14-hydroxyl in the known compound mutilin (Y = H in formula (4)), in practice it is desirable to use an intermediate in which the 11-hydroxyl is protected, such as a compound of formula (4) (Y ≠ H) or (5).

Suitable compounds as formula (4) include 11-O-acyl mutilin derivatives, e.g. mutilin 11-acetate (Y = Ac in formula (4)) (A J Birch, C W Holzapfel, R W Richards, Tetrahedron (Suppl.), 1966, 8, Part II, 359) or mutilin 11-dichloroacetate or mutilin 11-trifluoroacetate. After formation of the 14-ester derivative, the 11-O-acyl group may be removed by selective hydrolysis (e.g. using NaOH in MeOH).

Formula (5) is (3R)-3-deoxo-11-deoxy-3-methoxy-11-oxo-4-epi-mutilin (H Berner, G Schulz and H Schneider, Tetrahedron, 1980, 36, 1807). After formation of the 14-ester, the intermediate may be converted into (3) by treatment with conc. HCl or Lukas reagent (conc. HCl saturated with $ZnCl_2$) in dioxane.

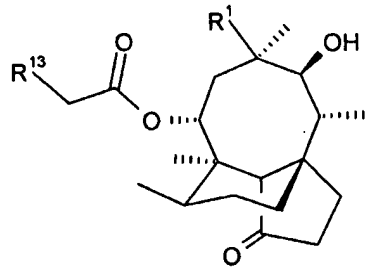
For preparation of 19,20-dihydro analogues (compounds of the above formulae in which R^1 = ethyl), before or after the esterification, of a compound of formula (4) or (5), a vinyl group R^1 may be reduced by hydrogenation over a palladium catalyst (e.g. 10% palladium-on-carbon) in a solvent such as ethyl acetate, ethanol, dioxane, or tetrahydrofuran.

Suitable hydroxy, carboxy and amino protecting groups are those well known in the art and which may be removed under conventional conditions and without disrupting the remainder of the molecule. A comprehensive discussion of the ways in which hydroxy, carboxy and amino groups may be protected and methods for cleaving the resulting protected derivatives is given in for example "Protective Groups in Organic Chemistry" (T.W. Greene and P.G.M. Wuts, Wiley-Interscience, New York, 2nd edition, 1991). Particularly suitable hydroxy protecting groups include, for example, triorganosilyl groups such as, for instance, trialkylsilyl and also organocarbonyl and organooxycarbonyl groups such as, for instance, acetyl, allyloxycarbonyl, 4-methoxybenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl. Particularly suitable carboxy protecting groups include alkyl

and aryl groups, for instance methyl, ethyl and phenyl. Particularly suitable amino protecting groups include alkoxycarbonyl, 4-methoxybenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl.

In cases where the intermediate of formula (4) (such as Y= acetyl) is used, a base-labile protecting group may conveniently be removed at the same time as the group Y is deprotected. In cases when the intermediate of formula (5) is used, an acid-labile protecting group may conveniently be removed at the same time as the compound (5) is converted into the compound (3).

Compounds of formula (3) wherein X is O, S, or NH and n is 0 may also be prepared by reaction of a compound of formula (7):



(7)

wherein R^{13} is a leaving group, such as 4-$MeC_6H_4SO_2O$, $MeSO_2O$, F_3CSO_2O, or Cl, with a compound of formula R^2-$(CH_2)_m$-XH, typically under the following conditions:

(a) Where X = O, the alcohol R^2-$(CH_2)_m$-OH is converted into the alkoxide by reaction with an inorganic base, such as sodium hydride, lithium hydride, sodium hexamethyldisilazide, or lithium hexamethyldisilazide, in a non-hydroxylic solvent, such as *N,N*-dimethylformamide or tetrahydrofuran, prior to reaction with the compound of formula (7);

(b) Where X = S, the thiol R^2-$(CH_2)_m$-SH is reacted with the compound of formula (7) in the presence of an inorganic base, such as sodium methoxide, sodium ethoxide, sodium hydride, sodium hexamethyldisilazide, or lithium hexamethyldisilazide, in a solvent such as 2-propanol, ethanol, methanol, *N,N*-dimethylformamide, or tetrahydrofuran.

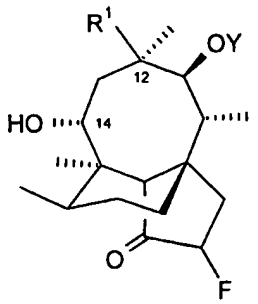
(c) Where X = NH, the amine R^2-$(CH_2)_m$-NH_2 is reacted with the compound of formula (7) in a solvent such as *N,N*-dimethylformamide or tetrahydrofuran, optionally in the presence of a base such as potassium carbonate, pyridine, *N,N*-di-(*iso*-propyl)-ethylamine, or triethylamine.

Compounds of formula (3) wherein X is CONH and n is 0 can also be prepared by reaction of a compound of formula (7), wherein R^{13} is amino, with a compound of formula R^2-$(CH_2)_m$-CO_2H, or an acylating agent derived therefrom, using one of the general methods for amide formation that are described in the chemical literature. General methods for amide formation are described by B C Challis and J A Challis in *Comprehensive Organic Chemistry*, Vol. 2, ed. I O Sutherland, pages 959-964 (Pergamon Press, Oxford, 1979).

The compounds of formula (7) are readily prepared from pleuromutilin or 19,20-dihydro-pleuromutilin. For example, the chloride, amine, and tosylate are described by K Riedl in *J. Antibiotics*, 1976, **29**, 132; and the tosylate and mesylate are described by H Egger and H Reinshagen in *J. Antibiotics*, 1976, **29**, 915.

Compounds of formula (3) wherein X is S(O) or SO_2 and R^1 is ethyl can also be prepared by treating the corresponding compound in which X = S with an oxidising agent; for example, 3-chloroperoxybenzoic acid in chloroform, or catalytic osmium tetroxide plus *N*-methylmorpholine *N*-oxide in tetrahydrofuran and tertiary-butanol.

In a further aspect the present invention provides a method for preparing compounds of the invention which comprises reacting an acylating agent, includuing a carbamoylating agent, with 2-fluoro-mutilin or 2-fluoro-19,20-dihydromutilin, preferably protected at the 11-hydroxy position, such as a compound of formula



where R^1 is ethyl or vinyl, and Y is hydrogen or a removable hydroxy-protecting group.

For example the acylating agent may be formed from the acid $HOCH_2CO_2H$, R-X-CH_2CO_2H, where X is O, S, or NR′ and R and R′ are individually an aliphatic or aromatic moiety, or R^2-$(CH_2)_m$-X-$(CH_2)_n$-CH_2CO_2H where each of n and m is independently between 0 and 2; X is selected from the group consisting of -O-, -S-, -S(O)-, -SO_2-, -NH-, CONH-, -CH_2-, and a bond; and R^2 is a non-aromatic monocyclic or bicyclic group containing one or two basic nitrogen atoms and attached through a ring carbon atom.

General methods for forming esters by this type of procedure are described by I O Sutherland in *Comprehensive Organic Chemistry*, Vol. 2, ed. I O Sutherland, pages 875-883 (Pergamon Press, Oxford, 1979). The acylating agent may be an acid chloride, acid bromide, a mixed anhydride, or an *N*-acyl-imidazole. The preferred agent is an acid chloride. General methods for forming such acylating agents are described in the chemical literature (see I O Sutherland, *loc. cit.*, and references therein).

More specific methods for forming the 14-acyloxy side chains are disclosed above for the formation of the compounds which are precursors to 14-acyloxy-2-diazo-mutilins. For example carbamoylation may be carried out as disclosed in WO 97/25309 or WO98/05659.

2-Fluoro-mutilins used in the above acyloxylation reaction may be prepared from mutilin via 2-hydroxy-methylene-mutilin and 2-diazo-mutilin, reacting the latter with a source of hydrogen fluoride, using the procedures described above.

Essentially the compounds of this invention may be prepared by introducing a 2-fluoro substituent to the mutilin nucleus before or after attachment of the 14-acyloxy group.

The compounds of the present invention may contain a chiral centre, and may therefore be obtained as a mixture of diastereoisomers or a single diastereoisomer. A single diastereoisomer may be prepared by separating such a mixture of diastereoisomers which has been synthesised using a racemic starting material, or by synthesis using an optically pure starting material.

The compounds of this invention may be in crystalline or non-crystalline form, and, if crystalline, may optionally be hydrated or solvated. When some of the compounds of this invention are allowed to crystallise or are recrystallised from organic solvents, solvent of crystallisation may be present in the crystalline product. This invention includes within its scope such solvates. Similarly, some of the compounds of this invention may be crystallised or recrystallised from solvents containing water. In such cases water of hydration may be present in the crystalline product. This invention includes within its scope stoichiometric hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation.

The compounds according to the invention are suitably provided in substantially pure form, for example at least 50% pure, suitable at least 60% pure, advantageously at least 75% pure, preferably at least 85% pure, more preferably at least 95% pure, especially at least 98% pure, all percentages being calculated as weight/weight. An impure or less pure form of a compound according to the invention may, for example, be used in the preparation of a more pure form of the same compound or of a related compound (for example a corresponding derivative) suitable for pharmaceutical use.

The present invention also includes pharmaceutically acceptable salts and derivatives of the compounds of the invention. Salt formation may be possible when one of the substituents carries an acidic or basic group. Salts may be prepared by salt exchange in conventional manner.

Acid-addition salts may be pharmaceutically acceptable or non-pharmaceutically acceptable. In the latter case, such salts may be useful for isolation and purification of the compound of the invention, or intermediates thereto, and will subsequently be converted into a pharmaceutically acceptable salt or the free base. Pharmaceutically acceptable acid-addition salts include those described by Berge, Bighley, and Monkhouse, *J. Pharm. Sci.*, 1977, **66**, 1-19. Suitable salts include the hydrochloride, maleate, and methanesulphonate; particularly the hydrochloride.

It will also be understood that where the compound of the invention contains a free carboxy moiety, it can form a zwitterion.

The compounds of the present invention and their pharmaceutically acceptable salts or derivatives have antimicrobial properties and are useful for the treatment of microbial infections in animals, especially mammals, including humans, in particular humans and domesticated animals (including farm animals). The compounds may be used for the treatment of infections caused by, for example, Gram-positive and Gram-negative bacteria and mycoplasmas, including, for example, Staphylococcus aureus, Staphylococcus epidermidis, Enterococcus faecalis, Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus pneumoniae, Haemophilius sp., Neisseria sp., Legionella sp., Chlamydia sp., Moraxella catarrhalis, Mycoplasma pneumoniae, and Mycoplasma gallisepticum.

The present invention provides a pharmaceutical composition comprising a compound of the invention or a pharmaceutically acceptable salt or derivative thereof together with a pharmaceutically acceptable carrier or excipient.

The present invention also provides a method of treating microbial infections in animals, especially in humans and in domesticated mammals, which comprises administering a compound of the invention or a pharmaceutically acceptable salt or derivative thereof, or a composition according to the invention, to a patient in need thereof.

The invention further provides the use of a compound of the invention or a pharmaceutically acceptable salt or derivative thereof in the preparation of a medicament for use in the treatment of microbial infections.

The present invention in particular provides a method of treating or preventing recurrent otitis media or recurrent sinusitis in humans , which comprises nasally administering a compound of the invention or a pharmaceutically acceptable salt or derivative thereof, or a composition according to the invention, to a patient in need thereof.

The present invention further provides a method of treatment of skin and soft tissue infections and in the treatment of acne in humans , which comprises topically administering a compound of the invention or a pharmaceutically acceptable salt or derivative thereof, or a composition according to the invention, to a patient in need thereof.

More generally, the compounds and compositions according to the invention may be formulated for administration in any convenient way for use in human or veterinary medicine, by analogy with other antibiotics.

The compounds and compositions according to the invention may be formulated for administration by any route, for example oral, topical or parenteral. The compositions may, for example, be made up in the form of tablets, capsules, powders, granules, lozenges, creams, syrups, or liquid preparations, for example solutions or suspensions, which may be formulated for oral use or in sterile form for parenteral administration by injection or infusion.

Tablets and capsules for oral administration may be in unit dosage form, and may contain conventional excipients including, for example, binding agents, for example, syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrollidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; and pharmaceutically acceptable wetting agents, for example

sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or another suitable vehicle before use. Such liquid preparations may contain conventional additives, including, for example, suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, oily esters (for example glycerine), propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and, if desired, conventional flavouring and colour agents.

Compositions according to the invention intended for topical administration may, for example, be in the form of ointments, creams, lotions, eye ointments, eye drops, ear drops, nose drops, nasal sprays, impregnated dressings, and aerosols, and may contain appropriate conventional additives, including, for example, preservatives, solvents to assist drug penetration, and emollients in ointments and creams. Such topical formulations may also contain compatible conventional carriers, for example cream or ointment bases, and ethanol or oleyl alcohol for lotions. Such carriers may constitute from about 1% to about 98% by weight of the formulation; more usually they will constitute up to about 80% by weight of the formulation.

Compositions according to the invention intended for topical administration, in addition to the above, may also contain a steroidal anti-inflammatory agent; for example, betamethasone.

Compositions according to the invention may be formulated as suppositories, which may contain conventional suppository bases, for example cocoa-butter or other glycerides.

Compositions according to the invention intended for parenteral administration may conveniently be in fluid unit dosage forms, which may be prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, may be either suspended or dissolved in the vehicle. In preparing solutions, the compound may be dissolved in water for injection and filter-sterilised before being filled into a suitable vial or ampoule, which is then sealed. Advantageously, conventional additives including, for example, local anaesthetics, preservatives, and buffering agents can be dissolved in the vehicle. In order to enhance the stability of the solution, the composition may be frozen after being filled into the vial, and the water removed under vacuum; the resulting dry lyophilised powder may then be sealed in the vial and a accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions may be prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilisation cannot be accomplished by filtration. The compound may instead be sterilised by exposure to ethylene oxide before being suspended in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in such suspensions in order to facilitate uniform distribution of the compound.

A compound or composition according to the invention is suitably administered to the patient in an antimicrobially effective amount.

A composition according to the invention may suitably contain from 0.1% by weight, preferably from 10 to 60% by weight, of a compound according to the invention (based on the total weight of the composition), depending on the method of administration.

The compounds according to the invention may suitably be administered to the patient at a daily dosage of from 1.0 to 50 mg/kg of body weight. For an adult human (of approximately 70 kg body weight), from 50 to 3000 mg, for example about 1500 mg, of a compound according to the invention may be administered daily. Suitably, the dosage for adult humans is from 5 to 20 mg/kg per day. Higher or lower dosages may, however, be used in accordance with normal clinical practice.

When the compositions according to the invention are presented in unit dosage form, each unit dose may suitably comprise from 25 to 1000 mg, preferable from 50 to 500 mg, of a compound according to the invention.

It is believed that the successful treatment of recurrent otitis media and recurrent sinusitis, is associated with the elimination or reduction of nasal carriage of pathogenic bacteria such as *S. aureus*, *H. influenzae*, *S. pneumonia* and *M. catarrhalis*, in particular colonisation of the nasospharynx by such organisms.

Accordingly, in the manufacture of a medicament for reducing or eliminating the nasal carriage of pathogenic organisms associated with recurrent otitis media, the medicament is preferably adapted for nasal administration, in particular, focussed delivery to the nasopharynx.

To lessen the risk of encouraging the development of resistant organisms, it is preferred to administer the drug on an intermittent, rather than a continual, basis.

In a suitable intermittent treatment regimen, drug substance is administered on a daily basis, for a small number of days, for instance from 2 to 10, suitably 3 to 8, more suitably about 5 days, the administration then being repeated after an interval, for instance, on a monthly basis over a period of months, for instance up to six months.

Less preferably, the drug substance may be administered on a continuing, daily basis, over a prolonged period, for instance several months.

Suitably drug substance is administered once or twice a day. Suitably, drug substance is administered during the winter months when bacterial infections such as recurrent otitis media and recurrent sinusitis tend to be more prevalent.

Suitably, drug substance is administered at a dosage of from 1 to 10mg, preferably from 3 to 8, typically about 5mg, in each nostril, twice a day.

The drug substance is administered to the nasopharynx, in particular the anterior nasopharynx.

Suitably, the drug substance is present in medicaments for use in the present invention in between 0.01 and 10%, preferably 0.1 and 5%, more preferably 1 and 5%. Suitable amounts include 2% and 4% by weight of the medicament. It is preferred to avoid low level dosages of drug substance as this might increase the risk of the development of resistant bacteria.

Preferred compositions for administration are adapted for focussed delivery to, and residence within, the nasopharynx. The term 'focussed delivery' is used to mean that the composition is delivered to the nasopharynx, rather than remaining within the nares. The term 'residence' within the nasopharynx is used to mean that the composition once delivered remains within the nasopharynx over a course of several hours, rather than being washed away more or less immediately. These two aspects may be conveniently studied by γ (gamma) ray scintigraphy. Suitable such compositions include sprays and creams.

The invention is illustrated by the following Examples.

Example 1

[(3R,4S)-1-azabicyclo [2.2.1] hept-3-ylcarbonyl] carbamic acid-2-fluoromutilin 14-ester (mixture of (2R) and (2S).

Step 1 Formylated derivatives of mutilin

The reaction was carried out similarly to that described by A.J. Birch, C.W. Holzapfel and R.W. Rickards (Tet (Suppl) 1996 8 part III 359). Mutilin (6 g) in toluene (330 ml) and methyl formate (100 ml) was treated with sodium methoxide (3 g) and stirred under argon for 8 hours. Ice-water (100 ml) was added, followed by 2N HCl (220 ml). The mixture was shaken and separated and the aqueous extracted with ether. The combined

organic was dried and evaporated and the residue chromatographed, eluting with ethyl acetate/hexane mixtures. First eluted was 2-hydroxymethylene mutilin 11,14-diformate (2.33 g) ^{1}HNMR ($CDCl_3$) *inter alia* 5.02 (1H,d), 5.77 (1H,d), 6.94 (1H,s), 7.89 (1H,s), 8.10 (1H,s). Second to be eluted was 2-hydroxymethylene mutilin 11-formate (3.0 g) : ^{1}HNMR ($CDCl_3$) *inter alia* 4.40 (1H, d), 5.11 (1H, d), 7.06 (1H,s) 8.25 (1H, d, J O.8Hz). Third to be eluted was a mixture (2:1) of 2-hydroxymethylene mutilin 14-formate and 2-hydroxymethylene mutilin (1.8 g).

Step 2 2-Diazomutilin 11-formate

A solution of 2- hydroxymethylene mutilin 11-formate (3.0 g) in dichloromethane (100 ml) was cooled to -10 °C under argon and treated with triethylamine (3.3 ml) and tosylazide (2.36 g). The mixture was left 3 hours at room temperature, washed with 0.5N HCl (100 ml), water and aqueous $NaHCO_3$, dried and evaporated. The title compound was obtained as yellow crystals (1.68 g); IR ($CHCl_3$) 3635, 2083, 1714 and 1670cm.

Step 3 2-(S)-Fluoromutilin 11-formate

A suspension of 2-diazomutilin 11-formate (1 g) in ether (15 ml) was cooled to -15 °C under argon and treated dropwise with hydrogen fluoride-pyridine (2 ml). The cooling bath was removed and stirring continued until the mixture was colorless (approx. 1 hour). After dilution with EtOAc (30 ml), the solution was washed with water (2 x 20 ml) and $NaHCO_3$ solution (20 ml), dried and evaporated. Chromatography, eluting with 5% EtOAc in CHCfsl$_3$, gave the title compound as white crystals (0.4g): MS (-ve ion electrospray) m/z 365 (M-H, 30%).

Step 4 [(3R, 4S)-1-azabicyclo [2.2.1] hept-3-ylcarbonyl] carbamic acid-2-(S)-fluoromutilin 14-ester 11-formate

(3R,4S)-Ethyl 1-azabicyclo[2.2.1]heptane-3-carboxylate (2.0 g I.F. Cottrell. D. Hands, D.J. Kennedy, K.J. Paul. S.H.B. Wright and K.Hoogsteen. J. Chem. Soc.Perkin Trans. 1. 1991. 1091-1097) was dissolved in concentrated hydrochloric acid and heated under

reflux for 5 hours. After cooling, the solution was evaporated under reduced pressure and the residue re-evaporated from toluene (x3). Drying over phosphorus pentoxide and trituration with cold ethyl acetate/methanol gave the hydrochloride salt of (3R,4S)-1-azabicyclo[2.2.1]heptane-3-carboxylic acid (1.2 g). 300 mg of this was suspended in dichloromethane (9 ml) under argon and treated with DMF (2 drops) and oxalyl chloride (0.52 ml) and stirred for 4 hours. The solution was evaporated, toluene (5 ml) added and evaporated and the residue taken up in dry dichloromethane (10 ml). This solution under argon was treated with 2-(S)-fluoromutilin 11-formate (0.3 g), silver cyanate (0.45 g) and triethylamine (0.21 ml) and stirred 18 hours. Aqueous $NaHCO_3$ (10ml) was added, the mixture stirred vigorously 5 mins and filtered through celite. The layers were separated, the organic dried and evaporated. Chromatography, eluting with chloroform/methanol/0.88NH3 (aq) (19:1:0:1), gave the title compound as a foam (0.2g);MS (+ve ion electrospray)m/z 533 (MH+, 60%), 141 (100%).

Step 5 [(3R, 4S)-1- azabicyclo [2.2.1] hept-3-ylcarbonyl] carbamic acid-2-fluoromutilin 14-ester (mixture of (2R) and (2S))

The product from Step 4 (0.19g) was dissolved in ethanol (6 ml) and treated dropwise over approx. 1 hour with a 0.5 M solution of KOH in ethanol. When 1.3 ml had been added, TLC showed complete loss of starting material. The solution was diluted with $CHCl_3$ (30 ml), washed with water (30 ml), dried and evaporated. Chromatography, eluting with chloroform/methanol/0.88NH_3 (aq)(92.5:7.5:0.75), gave the title mixture as a foam (0.11 g): MS (+ve ion electrospray) m/z 505 (MH^+, 20%), 141 (100%).

Example 2

[(3R, 4S)-1- azabicyclo[2.2.1]hept-3-ylcarbonyl]carbamic acid-2-(S)-fluoromutilin 14-ester hydrochloride

Step 1 2-Hydroxymethylenemutilin

A mixture of 2- hydroxymethylenemutilin 11,14-diformate (2.33 g) and [2-hydroxymethylenemutilin 14-formate + 2- hydroxymethylenemutilin](1.8 g) (see Example 1, Step 1) was dissolved in ethanol (30 ml) and treated with 0.5NKOH in ethanol (60 ml). After 1 hour the solution was diluted with ethyl acetate (200 ml), washed with 0.2N HCl (120 ml) and water (100 ml), dried and evaporated to provide 2-hydroxymethylenemutilin as a foam (3.6 g); ^{1}HNMR ($CDCl_3$)*inter alia* 3.45 (1H,d), 4.37 (1H, d), 6.97 (1H,s).

Step 2 2-Diazomutilin

A solution of 2- hydroxymethylenemutilin (3.6 g) in dichloromethane was cooled to -10°C under argon, treated with triethylamine (4.6 ml) and tosyl azide (3.55 g) and warmed to room temperature. After 6 hours the solution was washed with 0.5N HCL (150 ml) and water (100 ml), dried and evaporated. The 2-diazomutilin was obtained as yellow crystals from ethyl acetate/hexane (1.7 g); IR (CHCl3) 3634,2082 and 1670 cm.

Step 3 2-(S)-fluoromutilin

Treatment of 2-diazomutilin with hydrogen fluoride-pyridine in the manner of Example 1, Step 3 gave the title compound as white crystals: MS (-ve ion electrospray) 397 ($M+OAc^-$, 100%), 337 ($M-H^-$, 30%).

Step 4 2-(S)-fluoromutilin 11-trifluoracetate

A solution of 2-(S)- fluoromutilin (2.18 g) in THF (80 ml)under argon was treated with trifluoracetyl imidazole (0.806 ml) and stirred for 22 hours. The mixture was concentrated to ca. 10 ml., diluted with ethyl acetate (50 ml) and water (50 ml), shaken and the layers separated. The organic was dried and evaporated. Chromatography of the residue, eluting with 15% EtOAc in hexane, gave the title compound (1.81 g) as a white foam: ^{1}H NMR ($CDCl_3$) *inter alia* 4.28 (1H, t, J 6.5 Hz), 4.68 (1H,dt,J52 and 7.7Hz), 4.90(1H,d,J6.7Hz).

Step 5 [(3R,4S)-1- azabicyclo[2.2.1]hept-3-ylcarbonyl] carbamic acid-2-(S)-fluoromutilin 14 ester 11-trifluoracetate

The product of Step 5 was reacted in the manner of Example 1, Step 4 to give the title compound as a white foam (62%): MS (+ve ion electrospray) 601 (MH^+, 100%).

Step 6 [(3R,4S)-1-azabicyclo[2.2.1]hept-3-ylcarbonyl] carbamic acid-2-(S)-fluoromutilin 14-ester hydrochloride

The product of Step 4 (1.5g) was dissolved in ethanol (150 ml), treated with saturated aqueous $NaHCO_3$ (150 ml) and stirred vigorously for 2 hours. Chloroform (400 ml) and water (400 ml) were added, the mixture shaken and separated. The organic was dried and evaporated and the residue chromatographed, eluting with chloroform/methanol/ $0.88NH_3$(aq) (94:6:0.6). After evaporation of solvent, the product was redissolved in chloroform (100 ml) and treated with 1M HCl in diethyl ether (2 ml). Solvent was evaporated to leave the title compound as white solid (1.31 g): MS (+ve ion electrospray) 546 (MH^++MeCN, 60%), 505 (MH^+, 100%).

Example 3

p-Methoxybenzoylcarbamic acid-2-(R)-fluoromutilin 14-ester and p-Methoxybenzoylcarbamic acid-2-(S)-fluoromutilin 14-ester

Step 1 p-Methoxybenzoylcarbamic acid-2-hydroxymethylene mutilin 14-ester 11-formate

p-Methoxybenzoylcarbamic acid mutilin 14-ester (Example 31 of PCT/EP 96/05874) was converted into the title compound in the manner of Example 1, Step 1.

Step 2 p-Methoxybenzoylcarbamic acid-2-diazomutilin 14-ester 11-formate

p-Methoxybenzoylcarbamic acid-2-hydroxymethylene mutilin 14-ester 11-formate was converted into the title compound in the manner of Example 1, Step 2: MS (-ve ion electrospray) 550 ($M-H^-$, 100%).

Step 3 p-Methoxybenzoylcarbamic acid-2-(S) fluoromutilin 14-ester 11-formate

A suspension of p-methoxybenzoylcarbamic acid-2-diazomutilin 14-ester 11-formate (0.276g) in diethyl ether (2.5 ml) was cooled to -15°C under argon and treated dropwise with hydrogen fluoride-pyridine (1 ml). The cooling bath was removed, and within 5 mins. a colorless solution had formed. This was diluted with EtOAc (20 ml), washed with water (2 x 20 ml), dried and evaporated. Chromatography, eluting with 30% EtOAc in hexane, gave the title compound as a white solid (0.11 g): MS (-ve ion electrospray) 542 ($M-H^-$, 100%), 365 (80%).

Step 4 p-Methoxybenzoylcarbamic acid-2-(R) fluoromutilin 14-ester and p-methoxybenzoylcarbamic acid-2-(S)-fluoromutilin 14-ester

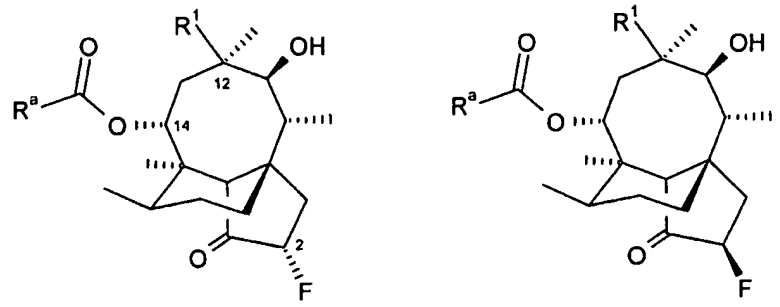
The product of Step 3 (0.11g) was dissolved in THF (2ml)/ethanol (2ml) and treated dropwise over 1 hour with 0.5M KOH in ethanol (0.8 ml). The solution was diluted with EtOAc (15 ml), washed with water (2 x 15 ml), dried and evaporated. Chromatography, eluting with 40% EtOAc in hexane, gave 2 products. First eluted was p-methoxybenzoylcarbamic acid-2-(S)-fluoromutilin 14-ester (0.026 g): MS (-ve ion electrospray) 514 ($M-H^-$, 100%).

Second eluted was p-methoxybenzoylcarbamic acid-2-(R)-fluoromutilin 14-ester (0.055 g): MS (-ve ion electrospray) 514 ($M-H^-$, 100%).

CLAIMS

1. A 14-acyloxy derivative of mutilin or 19,20-dihydromutilin having a 2-fluoro substituent.

2. A compound of structure



in which R^1 is vinyl or ethyl, and R^a.CO.O- is an acyloxy group.

3. A compound according to claim 2 in which the acyloxy group is $HOCH_2CO_2$- or R-X-CH_2CO_2-, where X is O, S, or NR' and R and R' are individually an aliphatic or aromatic moiety.

4. A compound according to claim 2 in which the acyloxy group is R^2-$(CH_2)_m$-X-$(CH_2)_n$-CH_2CO_2- where each of n and m is independently from 0 to 2; X is selected from -O-, -S-, -S(O)-, -SO_2-, -NH-, CONH-, -CH_2-, and a bond; and R^2 is a non-aromatic monocyclic or bicyclic group containing one or two basic nitrogen atoms and attached through a ring carbon atom.

5. A compound according to claim 2 in which the acyloxy group is carbamoyl.

6. A compound according to claim 5 in which the acyloxy group is $R^3R^4NCO_2$- in which:

R^3 and R^4 are the same or different groups selected from

hydrogen;

a straight or branch chained, saturated or unsaturated, optionally substituted, C_1 to C_6 hydrocarbon group;

a saturated or unsaturated, optionally substituted, C_3 to C_8 cyclic hydrocarbon group;

an optionally substituted heterocyclic group;

an optionally substituted aryl group;

or together form an optionally substituted cyclic group of 3 to 8 ring atoms, optionally, containing one additional heteroatom selected from N, O and S, and optionally fused to a hydrocarbon ring, a heterocyclic group or an aromatic group; or

R^3 is one of the above monovalent groups and R^4 is a group selected from SO_2R^5, COR^6, OR^6 and NR^7R^8 where

R^5 is selected from a straight or branch chained, saturated or unsaturated, optionally substituted, C_1 to C_6 hydrocarbon group; a saturated or unsaturated, optionally substituted, C_3 to C_8 cyclic hydrocarbon group; an optionally substituted heterocyclic group; an optionally substituted aryl group; an optionally substituted C_1 to C_6 alkyl amino group; and an optionally substituted aryl amino group;

R^6 is selected from hydrogen; a straight or branch chained, saturated or unsaturated, optionally substituted, C_1 to C_6 hydrocarbon group; a saturated or unsaturated, optionally substituted, C_3 to C_8 cyclic hydrocarbon group; an optionally substituted heterocyclic group; and an optionally substituted aryl group;

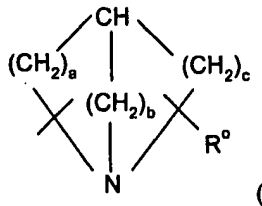
R^7 and R^8 are the same or different groups selected from hydrogen; a straight or branch chained, saturated or unsaturated, optionally substituted, C_1 to C_6 hydrocarbon group; a saturated or unsaturated, optionally substituted, C_3 to C_8 cyclic hydrocarbon group; an optionally substituted heterocyclic group, and an optionally substituted aryl group; or together form an optionally substituted cyclic group of 3 to 8 ring atoms, optionally containing one additional heteroatom selected from N, O and S, and optionally fused to a hydrocarbon ring, a heterocyclic group or an aromatic group.

7. A compound according to claim 5 in which the N-atom of the carbamoyl group is acylated by a group which includes an azabicyclic moiety.

8. A compound according to claim 7 in which the acyloxy group is $R^9CONHCO_2$- in which R^9 is a group R^{10}, $R^{10}CH_2$-, or $R^{11}R^{12}C$=CH-; wherein R^{10} is an azabicyclic ring system or R^{11} and R^{12} together with the carbon atom to which they are attached form an azabicyclic ring system.

9. A compound according to claim 8 in which the azabicyclic ring system is a bridged or fused non-aromatic ring system attached via a bridgehead or non-bridgehead ring carbon atom and containing one bridgehead nitrogen atom as the sole hetero ring atom.

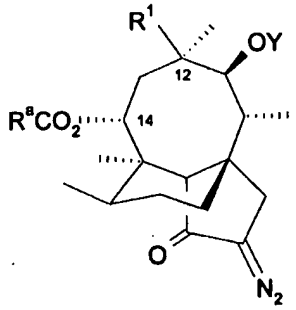
10. A compound according to claim 9 in which the azabicyclic ring system is represented by formula (I):



(I)

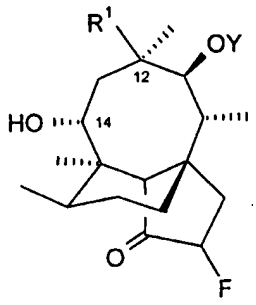
wherein R^7 represents one or more optional substituents as set out above and each of a, b and c is between 0 and 4, such that any one ring has between 5 and 10 ring atoms.

11. A method for preparing a compound as claimed in any one of claims 1-10 which comprises reacting a compound of formula



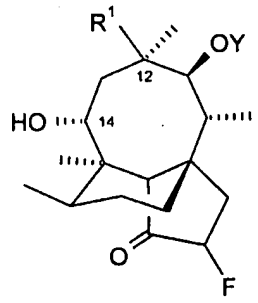
where R^1 is ethyl or vinyl, R^a.CO.O- is an acyloxy group, and Y is hydrogen or a removable hydroxy-protecting group,
with a source of hydrogen fluoride.

12. A method for preparing a compound as claimed in any one of claims 1-10 which comprises reacting an acylating agent, including a carbamoylating agent, with a compound of formula



where R^1 is ethyl or vinyl, and Y is hydrogen or a removable hydroxy-protecting group.

13. A compound of formula:



where R^1 is ethyl or vinyl, and Y is hydrogen or a removable hydroxy-protecting group

14. A method of treating microbial infections in animals, especially in humans and in domesticated mammals, which comprises administering a compound according to any one of claims 1 to 10 or a pharmaceutically acceptable salt or derivative thereof, or a composition according to the invention, to a patient in need thereof.

15 A method of treating or preventing recurrent otitis media or recurrent sinusitis in humans , which comprises nasally administering a compound according to any one of claims 1 to 10 or a pharmaceutically acceptable salt or derivative thereof, or a composition according to the invention, to a patient in need thereof.

16. A method of treatment of skin and soft tissue infections and in the treatment of acne in humans , which comprises topically administering a compound according to any one of claims 1 to 10 or a pharmaceutically acceptable salt or derivative thereof, or a composition according to the invention, to a patient in need thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/02575

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C69/013 C07C271/32 A61K31/215 A61K31/27 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 25309 A (HUNT ERIC ;HINKS JEREMY DAVID (GB); SMITHKLINE BEECHAM PLC (GB); T) 17 July 1997 (1997-07-17) cited in the application ---	1-16
A	WO 98 05659 A (NAYLOR ANTOINETTE ;HUNT ERIC (GB); SMITHKLINE BEECHAM PLC (GB); TA) 12 February 1998 (1998-02-12) cited in the application -----	1-16

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 November 1999	03. 12. 99

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Janus, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int. ..ational application No.
PCT/GB 99/02575

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 14-16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 99/02575

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